CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040252

Trade Name : CARISOPRODOL AND ASPIRIN TABLETS USP

Generic Name: Carisoprodol and Aspirin Tablets USP 200mg/325mg

Sponsor : Amide Pharmaceutical, Inc.

Approval Date: December 10, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040252

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040252

APPROVAL LETTER

ANDA 40-252

DEC 10 1997

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 E. Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application dated March 20, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Carisoprodol and Aspirin Tablets USP, 200 mg/325 mg.

Reference is also made to your amendments dated August 22, November 28, December 3, and December 8, 1997.

Your application contains a patent certification to patent 4,534,973 under Section 505(j)(2)(A)(vii)(IV) of the Act. Section 505(j)(4)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Amide Pharmaceutical, Inc. has complied with the requirements of Section 505(j)(2)(B) of the Act. No action for patent infringement was brought against Amide Pharmaceutical, Inc. within the statutory forty-five day period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Carisoprodol and Aspirin Tablets USP, 200 mg/325 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Soma® Compound Tablets, 200 mg/325 mg of Wallace Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

12/10/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040252

FINAL PRINTED LABELING

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-252

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc. (AP)
101 East Main Street
Little Falls, NJ 07424

4. BASIS OF SUBMISSION
The listed drug product is Soma[R] Compound by Wallace Laboratories (Division of Carter-Wallace, Inc.) approved in NDA # 12-365 005.

No exclusivity exists for the drug product according to 17th edition of the Approved Drug Products with Therapeutic Equivalence Evaluation.

AP submitted Patent Certification on page 10 to certify that, in their opinion, patent # 4,534,973 held by Wallace Laboratories and expiring on July 31, 2004 will not be infringed upon manufacture, use or sale by their Carisoprodol/Aspirin Tablets.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Carisoprodol and Aspirin Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 3-20-97
Accepted for filing on: 3-21-97 (Acknowledgment letter date: 5-1-97)
* Minor Amendment: 8-22-97 (Response to NA letter dated 8-6-97.

10. PHARMACOLOGICAL CATEGORY
Used for relief of painful musculoskeletal conditions.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

(b)4 - Confidential Business

13. DOSAGE FORM
Tablets

14. POTENCY
Carisoprodol 200 mg
Aspirin 325 mg

15. CHEMICAL NAME AND STRUCTURE
Carisoprodol is N-isopropyl-2-methyl-2 propyl-1,3-propanediol dicarbamate
Aspirin is 2-(Acetyloxy) benzoic Acid.

Structures: See USP 23

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. AP clarified that they will use grade

(b)4 - Confidential Business

2. Amide Pharmaceutical has submitted adequate information regarding all pertinent aspects required to approved this application with respect to manufacturing, control and stability testing, and FPL. The bio status is acceptable.
3. Status for EER submitted for all the facilities is acceptable on 8-5-97.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
9-19-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040252

CHEMISTRY REVIEW(S)

Amide
PHARMACEUTICAL, INC.

NDC 52152-137-02

CARISOPRODOL AND ASPIRIN TABLETS USP 200 mg/325 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Carisoprodol ..... 200 mg
Aspirin ..... 325 mg

Usual Adult Dosage: 1 or 2 tablets, four times daily. See accompanying literature for full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.
Protect from moisture.

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 52152-137-02 9

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

DEC 10 1997

Control No.:
Exp. Date:

7868-00

Amide
PHARMACEUTICAL, INC.

NDC 52152-137-04

CARISOPRODOL AND ASPIRIN TABLETS USP 200 mg/325 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Each Tablet Contains:
Carisoprodol ..... 200 mg
Aspirin ..... 325 mg

Usual Adult Dosage: 1 or 2 tablets, four times daily. See accompanying literature for full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.
Protect from moisture.

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 52152-137-04 3

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

DEC 10 1997

Control No.:
Exp. Date:

7867-00

Carisoprodol-Stupor, coma, shock, respiratory depression, and, very rarely, death. Overdosage with carisoprodol in combination with alcohol, other CNS depressants, or psychotropic agents can have additive effects, even when one of the agents has been taken in the usually recommended dosage.

Aspirin-Headache, tinnitus, hearing difficulty, dim vision, dizziness, lassitude, hyperpnea, rapid breathing, thirst, nausea, vomiting, sweating, and occasionally diarrhea are characteristic of mild to moderate salicylate poisoning. Salicylate poisoning should be considered in children with symptoms of vomiting, hyperpnea, and hyperthermia.

Hyperpnea is an early sign of salicylate poisoning, but dyspnea supervenes at plasma levels above 50 mg/dL. These respiratory changes eventually lead to serious acid-base disturbances. Metabolic acidosis is a constant finding in infants but occurs in older children only with severe poisoning; adults usually exhibit respiratory alkalosis initially and acidosis terminally.

Other symptoms of severe salicylate poisoning include hyperthermia, dehydration, delirium, and mental disturbances. Skin eruptions, GI hemorrhage, or pulmonary edema are less common. Early CNS stimulation is replaced by increasing depression, stupor, and coma. Death is usually due to respiratory failure or cardiovascular collapse.

Treatment-*General:* Provide symptomatic and supportive treatment, as indicated. Any drug remaining in the stomach should be removed using appropriate procedures and caution to protect the airway and prevent aspiration, especially in the stuporous or comatose patient. Incomplete gastric emptying with delayed absorption of carisoprodol has been reported as a cause for relapse. Should respiration or blood pressure become compromised, respiratory assistance, central nervous system stimulants, and pressor agents should be administered cautiously, as indicated.

Carisoprodol: The following have been used successfully in overdosage with the related drug meprobamate: diuretics, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis (see CLINICAL PHARMACOLOGY). Careful monitoring of urinary output is necessary and caution should be taken to avoid overhydration. Carisoprodol can be measured in biological fluid by gas chromatography (Dougias, J.F., et al: *J Pharm Sci* 58:145, 1969).

Aspirin-Since there are no specific antidotes for salicylate poisoning, the aim of treatment is to enhance elimination of salicylate and prevent or reduce further absorption; to correct any fluid, electrolyte or metabolic imbalance; and to provide general and cardiorespiratory support. If acidosis is present, intravenous sodium bicarbonate must be given, along with adequate hydration, until salicylate levels decrease to within the therapeutic range. To enhance elimination, forced diuresis and alkalinization of the urine may be beneficial. The need for hemoperfusion or hemodialysis is rare and should be used only when other measures have failed.

DOSAGE AND ADMINISTRATION-*Usual Adult Dosage:* 1 or 2 tablets, four times daily.

Not recommended for use in children under age twelve (see PRECAUTIONS).

HOW SUPPLIED- Carisoprodol and Aspirin Tablets 200 mg/ 325 mg are red and white, round, unscored, convex, two-layered tablets and are inscribed on one side with "A137". The tablets are available in bottles of 100 and 500.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight container.

Caution: Federal Law prohibits dispensing without a prescription.

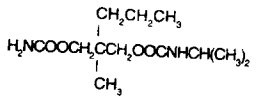
DEC 10 1997

8/97

MANUFACTURED BY:
AMIDE PHARMACEUTICAL, INC.
LITTLE FALLS, NJ 07424 USA

DESCRIPTION- Carisoprodol and Aspirin Tablets USP is a combination product containing carisoprodol, a centrally-acting muscle relaxant, plus aspirin, an analgesic with antipyretic and antiinflammatory properties.

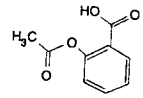
Chemically, carisoprodol is (±)-2-Methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate. Carisoprodol is a white, crystalline powder, having a mild, characteristic odor and a bitter taste. It is very slightly soluble in water; freely soluble in alcohol, in chloroform, and in acetone. Its molecular formula is $C_{12}H_{24}N_2O_4$, with a molecular weight of 260.34. The structural formula is:



7869-00

CARISOPRODOL AND ASPIRIN TABLETS USP

Chemically, aspirin is salicylic acid acetate. It can appear as white crystals, commonly tabular or needle-like, or white crystalline powder. It is odorless or has a faint odor. It is slightly soluble in water; freely soluble in alcohol; soluble in chloroform and in ether; sparingly soluble in absolute ether. Its molecular formula is $C_9H_8O_4$, with a molecular weight of 180.16. The structural formula is:



Each tablet, for oral administration, contains 200 mg of carisoprodol and 325 mg of aspirin. In addition, each tablet contains the following inactive ingredients: FD&C Red #40 aluminum lake, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, silicon dioxide, sodium starch glycolate, corn starch, stearic acid and zinc stearate.

CLINICAL PHARMACOLOGY-Carisoprodol: Carisoprodol is a centrally-acting muscle relaxant that does not directly relax tense skeletal muscles in man. The mode of action of carisoprodol in relieving acute muscle spasm of local origin has not been clearly identified, but may be related to its sedative properties. In animals, carisoprodol has been shown to produce muscle relaxation by blocking interneuronal activity and depressing transmission of polysynaptic neurons in the spinal cord and in the descending reticular formation of the brain. The onset of action is rapid and lasts four to six hours.

Carisoprodol is metabolized in the liver and is excreted by the kidneys. It is dialyzable by peritoneal and hemodialysis.

Aspirin: Aspirin is a nonnarcotic analgesic with antiinflammatory and antipyretic activity. Inhibition of prostaglandin biosynthesis appears to account for most of its antiinflammatory and for at least part of its analgesic and antipyretic properties.

Aspirin is rapidly absorbed and almost totally hydrolyzed to salicylic acid following oral administration. Although aspirin has a half-life of only about 15 minutes, the apparent biologic half-life of salicylic acid in the therapeutic plasma concentration range is between 6 and 12 hours. Salicylic acid is eliminated by renal excretion and by biotransformation to inactive metabolites. Clearance of salicylic acid in the high-dose range is sensitive to urinary pH (see ***Drug Interactions)*** and is reduced by renal dysfunction.

INDICATIONS AND USAGE- Carisoprodol and Aspirin Tablets are indicated as an adjunct to rest, physical therapy, and other measures for the relief of pain, muscle spasm, and limited mobility associated with acute, painful musculoskeletal conditions.

CONTRAINDICATIONS- Acute intermittent porphyria; bleeding disorders; allergic or idiosyncratic reactions to carisoprodol, aspirin, or related compounds.

WARNINGS- On very rare occasions, the first dose of carisoprodol has been followed by an idiosyncratic reaction with symptoms appearing within minutes or hours. These may include extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. Although symptoms usually subside over the course of the next several hours, discontinue Carisoprodol and Aspirin Tablets and initiate appropriate supportive and symptomatic therapy, which may include epinephrine and/or antihistamines. In severe cases, corticosteroids may be necessary. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock.

The effects of carisoprodol with agents such as alcohol, other CNS depressants, or psychotropic drugs may be additive. Appropriate caution should be exercised with patients who may take one or more of these agents simultaneously with Carisoprodol and Aspirin Tablets.

PRECAUTIONS-General: To avoid excessive accumulation of carisoprodol, aspirin, or their metabolites, use Carisoprodol and Aspirin Tablets with caution in patients with compromised liver or kidney function, or in elderly or debilitated patients (see CLINICAL PHARMACOLOGY).

Use with caution in patients with history of gastritis or peptic ulcer, in patients on anticoagulant therapy, and in addiction-prone individuals.

Information for Patients: Caution patients that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a motor vehicle or operating machinery.

Caution patients with a predisposition for gastrointestinal bleeding that concomitant use of aspirin and alcohol may have an additive effect in this regard.

Caution patients that dosage of medications used for gout, arthritis, or diabetes may have to be adjusted when aspirin is administered or discontinued (see ***Drug Interactions).***

Drug Interactions: Clinically important interactions may occur when certain drugs are administered concomitantly with aspirin or aspirin-containing drugs.

1. *Oral Anticoagulants-* By interfering with platelet function or decreasing plasma prothrombin concentration, aspirin enhances the potential for bleeding in patients on anticoagulants.
2. *Methotrexate-*aspirin enhances the toxic effects of this drug.
3. *Probenecid and Sulfinpyrazone-*large doses of aspirin reduce the uricosuric effect of both drugs. Renal excretion of salicylate may also be reduced.
4. *Oral Antidiabetic Drugs-*enhancement of hypoglycemia may occur.
5. *Antacids-*to the extent that they raise urinary pH, antacids may substantially decrease plasma salicylate concentrations; conversely, their withdrawal can result in a substantial increase.
6. *Ammonium Chloride-*this and other drugs that acidify a relatively alkaline urine can elevate plasma salicylate concentrations.
7. *Ethyl Alcohol-*enhanced aspirin-induced fecal blood loss has been reported.
8. *Corticosteroids-*salicylate plasma levels may be decreased when adrenal corticosteroids are given, and may be increased substantially when they are discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies have been done with Carisoprodol and Aspirin Tablets.

Pregnancy-Teratogenic Effects: Pregnancy Category C. Adequate animal reproduction studies have not been conducted with Carisoprodol and Aspirin Tablets. It is also not known whether Carisoprodol and Aspirin Tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Carisoprodol and Aspirin Tablets should be given to a pregnant woman only if clearly needed. Studies in rodents have shown salicylates to be teratogenic when given in early gestation, and embryocidal when given in later gestation in doses considerably greater than usual therapeutic doses in humans. Studies in women who took aspirin during pregnancy have not demonstrated an increased incidence of congenital abnormalities in the offspring.

Labor and Delivery: Ingestion of aspirin near term or prior to delivery may prolong delivery or lead to bleeding in mother, fetus, or neonate.

Nursing Mothers: Carisoprodol is excreted in human milk in concentrations two-to-four times that in maternal plasma. Aspirin is excreted in human milk in moderate amounts and can produce a bleeding tendency in nursing infants. Because of the potential for serious adverse reactions in nursing infants a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of twelve have not been established.

ADVERSE REACTIONS- If severe reactions occur, discontinue Carisoprodol and Aspirin Tablets and initiate appropriate symptomatic and supportive therapy.

The following side effects which have occurred with the administration of the individual ingredients alone may also occur with the combination.

Carisoprodol: *Central Nervous System-*Drowsiness is the most frequent complaint and along with other CNS effects may require dosage reduction. Observed less frequently are dizziness, vertigo, and ataxia. Tremor, agitation, irritability, headache, depressive reactions, syncope, and insomnia have been infrequent or rare.

Idiosyncratic - Idiosyncratic reactions are very rare. They are usually seen within the period of the first to fourth dose in patients having had no previous contact with the drug (see WARNINGS).

*Allergic-*Skin rash, erythema multiforme, pruritus, eosinophilia, and fixed drug eruptions with cross-reaction to meprobamate have been reported. If allergic reactions occur, discontinue Carisoprodol and Aspirin Tablets and treat symptomatically. In evaluating possible allergic reactions, also consider allergy to excipients (information on excipients is available to physicians on request).

*Cardiovascular-*Tachycardia, postural hypotension, and facial flushing.

*Gastrointestinal-*Nausea, vomiting, epigastric distress, and hiccup.

*Hematologic-*No serious blood dyscrasias have been attributed to carisoprodol alone. Leukopenia and pancytopenia have been reported, very rarely, in situations in which other drugs or viral infections may have been responsible.

Aspirin: The most common adverse reactions associated with the use of aspirin have been gastrointestinal, including nausea, vomiting, gastritis, occult bleeding, constipation, and diarrhea. Gastric erosion, angioedema, asthma, rash, pruritus, and urticaria have been reported less commonly. Tinnitus is a sign of high serum salicylate levels (see OVERDOSAGE).
Aspirin Intolerance-Allergic type reactions in aspirin sensitive individuals may involve the respiratory tract or the skin. Symptoms of the former range from rhinorrhea and shortness of breath to severe asthma, and the latter may consist of urticaria, edema, rash, or angioedema (giant hives). These may occur independently or in combination.

DRUG ABUSE AND DEPENDENCE-

Abuse: In clinical use, abuse has been rare.

Dependence: In clinical use, dependence with Carisoprodol and Aspirin Tablets has been rare, and there have been no reports of significant abstinence signs. Nevertheless, the following information on the individual ingredients should be kept in mind.

Carisoprodol - In dogs, no withdrawal symptoms occurred after abrupt cessation of carisoprodol from dosages as high as 1 gm/kg/day. In a study in man, abrupt cessation of 100 mg/kg/day (about five times the recommended daily adult dosage) was followed in some subjects by mild withdrawal symptoms such as abdominal cramps, insomnia, chills, headache, and nausea. Delirium and convulsions did not occur (see PRECAUTIONS).

OVERDOSAGE-*Signs and Symptoms:* Any of the following which have been reported with the individual ingredients may occur and may be modified to a varying degree by the effects of the other ingredients present in Carisoprodol and Aspirin Tablets.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040252

BIOEQUIVALENCE REVIEW(S)

ANDA 40-252

JUL 25 1997

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

Dear Ms. Shah:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Carisoprodol and Aspirin Tablets USP, 200 mg/ 325 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 16 1997

Carisoprodol and Aspirin Tablets, USP
200/325mg Tablets
ANDA #40-252
Reviewer: James Chaney
WP# 40252DW.397

Amide Pharmaceutical, Inc.
Little Falls, NJ
Submission Date:
March 20, 1997

REVIEW OF DISSOLUTION DATA AND A WAIVER REQUEST

I. INTRODUCTION

Amide Pharmaceutical, Inc. has submitted comparative dissolution data on its drug product, Carisoprodol and aspirin Tablets, USP, 200/325 mg comparing it to the reference, Wallace's Soma Compound®, 200/325 mg tablet, in support of a request waiver of *in vivo* bioequivalence requirements. Carisoprodol produces muscle relaxation and is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions. The usual adult dose is one 200/325 mg tablet, three times daily and at bedtime.

II. FORMULATION

The formulation of Amide Pharmaceuticals' Carisoprodol and Aspirin 200 mg/325 mg Tablets is shown in Table 1.

III. DISSOLUTION

The dissolution method, USP apparatus II (paddle), 900 mL water, 75 rpm, Q=NLT (b)4 of each component dissolved in 45 minutes, as recommended by USP XXIII was followed. The dissolution data comparing the test (Amide) and reference (Wallace Laboratories) is given in Table 2. The batch size was (b)4 for the lot on which the reported comparative dissolution testing was done.

IV. COMMENTS

1. The comparative dissolution testing data on the test and reference products meet the USP dissolution specifications.
2. The test product does not contain any inactive ingredients that may cause a bioequivalence problem.
3. The reference product, Wallace's Soma Compound®, 200/325 mg tablet (carisoprodol and aspirin tablet, USP, 200/325 mg) is classified AB in Approved Drug Products with Therapeutic Equivalence Evaluations, 17th Edition ("Orange Book"). However, since the dissolution testing is acceptable there would be no need to conduct an *in vivo* bioequivalence study because the drug product is included in the "Orange Book" under the section of "Drug products which must demonstrate *in vivo* bioavailability only if product fails to achieve adequate dissolution".

4. Satisfactory content uniformity data was submitted for the lot used in the dissolution testing.

V. RECOMMENDATIONS

1. The dissolution testing conducted by Amide Pharmaceutical, Inc. on its Carisoprodol/Aspirin 200 mg/325mg tablet formulation, lot # 6265A and Soma Compound® Tablet, lot # 5L1076A, manufactured by Wallace Laboratories is acceptable. The waiver of *in vivo* bioequivalence study requirements for the 200mg/325mg carisoprodol/aspirin test product is granted. The 200mg/325mg carisoprodol/aspirin test product is therefore deemed bioequivalent to the 200mg/325mg Carisoprodol/Aspirin, Soma Compound® Tablet manufactured by Wallace Laboratories.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL water at 37°C using USP XXIII apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

   Not less than (b)4 of the labeled amount of both the components in the dosage form should be dissolved in 45 minutes.

The firm should be informed of the recommendations.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 7/7/97

Concur: /S/ Date: 7/16/97
Nicholas M. Fleischer, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 40-252 (original, duplicate), ~~HFD-630 (Hare)~~, HFD-652 (Huang, Chaney), HFD-650 (Director), Drug File, Division File

JEC/070397/WP #40252DW.397

Table 1. Composition of Amide Pharmaceutical' Carisoprodol/Aspirin 200/325mg Tablets, Lot # Lot # 6265A

	Per Tablet (mg)
PART A - Carisoprodol Layer	
Carisoprodol, USP	200.0
Lactose Monohydrate, NF	
Sodium Starch Glycolate, NF	
FD&C Red #40 Aluminum Lake,	(b)4 -
*Purified Water, USP	
Microcrystalline Cellulose 101, NF	
Sodium Starch Glycolate, NF	
Stearic Acid, NF	
Zinc Stearate, USP	
(b)4 - Confidential Business	
TOTAL NET WEIGHT OF PART A	**300.0**
PART B - Aspirin Layer	
(b)4 - Confidential Business	
TOTAL NET WEIGHT OF PART B	**380.0**
TOTAL NET WEIGHT OF PART A & B	**680.0**

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): Carisoprodol and aspirin tablets, USP
Dose Strength: 200/325 mg
ANDA No.: 40-252
Firm: Amide Pharmaceutical, Inc.
Submission Date: 03/20/97
File Name: 40252DW.397

I. Conditions for Dissolution Testing:

USP Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: Water
Volume: 900 mL
Specifications: NLT (b)4 of each component in 45 min
Reference Drug: Wallace's Soma Compound®, 200/325 mg tablet
Assay Methodology: (b)4 -

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 6265A Strength (mg) 200/325			Reference Product Lot # 5L1076A Strength (mg) 200/325		
	Carisoprodol					
	Mean %	Range	%CV	Mean %	Range	%CV
20	93.9	(b)4 - Confidential Business	1.2	71.0	(b)4 - Confidential Business	1.6
30	94.0		1.1	79.7		1.8
45	94.8		0.7	86.6		1.6
	Aspirin					
	Mean %	Range	%CV	Mean %	Range	%CV
20	96.4	(b)4 - Confidential Business	1.0	100.8	(b)4 - Confidential Business	1.2
30	96.6		1.2	99.0		1.4
45	95.5		0.9	97.2		1.2